REMARKS/ARGUMENTS

Claims 1-16 are pending in the instant application. The pending claims have not been amended, and accordingly, claims 1-16 will remain pending upon entry of the instant remarks/arguments into the record. *No new matter has been added.*

Applicants wish to acknowledge and indicate their appreciation for the Examiner's willingness to engage in multiple telephone conversations undertaken in order to clarify statements of the Advisory Action.

Moreover, amendment and/or cancellation of the claims during pendency of the application are not to be construed as acquiescence to any of the objections/rejections set forth in any Office Action, and were done solely to expedite prosecution of the application. Applicants submit that claims were not added or amended during the prosecution of the instant application for reasons related to patentability. Applicants reserve the right to pursue the claims as originally filed, subsequently amended or added, or similar claims, in this or one or more subsequent patent applications.

Claims Rejections – 35 U.S.C. §103

Applicants appreciate Examiner Gitomer's reconsideration and withdrawal of the rejection of claims 1-16 under 35 U.S.C. §103(a) as unpatentable over Ross et al., as noted in the Advisory Action of March 18, 2008.

However, according to the Advisory Action, claims 1-16 remain rejected under 35 U.S.C. §103(a) as being unpatentable over Lee et al. (WO 00/70334). In this regard, Applicants' representative, in a telephone conversation with Examiner Gitomer undertaken in order to clarify statements of the Advisory Action that seemed contradictory, established to the satisfaction of Examiner Gitomer that **the disclosure of MALDI in Lee did not amount to the disclosure of digests of *large* molecules that would produce *small* molecules**. However, Examiner Gitomer suggested that the disclosure of the surfactants useful in the present invention in the analysis of large molecules

made obvious the instantly claimed invention directed to small molecules. Applicants respectfully disagree.

Applicants respectfully assert that the analysis of large molecules does not suggest or make obvious the solubilization, analysis, separation, purification and/or characterization of ***small*** molecules, by the simple fact that these molecules are clearly held in separate regard in the art. For example, Applicants enclose herewith Exhibit A, an article entitled "Introduction to Biological Production of Large Molecule Pharmaceuticals," published by Thermo Fisher Scientific © 2007 as a sales publication for scientific discovery-type services and products. The article clearly shows the ordinarily skilled artisan's appreciation for the significant differences between small and large molecules (even in 2007) and their requirement for separate treatment /consideration (*e.g.*, particularly, see the section starting on page entitled "Biopharmaceutical Vitality"). Small and large molecules behave differently and are rarely characterized by identical techniques of analysis. As such, there would be no reason that the ordinarily skilled artisan would consider a technique of analysis established for large molecules as useful for small molecule analysis, as recited in the pending claims.

The ordinarily skilled artisan understands from the outset, *i.e.*, synthesis, that small and large molecules are not treated equivalently, as they are, in fact, typically synthesized in completely disparate ways. Separation techniques, such as chromatography, and conditions under which such separations occur are most often completely distinct. Moreover, solvents and chromatographic media for such separations are rarely identical. In fact, when small and large molecules are present in the same biological matrix, the separate chemical characteristics (*i.e.*, with respect to the chromatographic media) typically allow larger (or complete) retention of one size while the other size passes through the media for an easy separation (*e.g.*, see again, the article noted above, page 4, last paragraph to page 5 first paragraph continued from page 4). Moreover, certain characterization methods, such as NMR, that are useful for small molecules may not even be useful for large molecules.

Large and small molecules have gained such a separate classification in the field of chemistry and pharmaceutical sciences that even in 2007, complete meetings/classes are still dedicated to investigating whether there are, in fact, overlaps between analyses that could be done on small and large molecules. In support of this assertion, Applicants attach herewith Exhibit B, which is an

advertisement for the 2007 Meeting of the American Association of Pharmaceutical Scientists (AAPS); wherein Exhibit B sets forth the description of a short course that indicates

> Because small and large molecules possess different attributes which are relied upon to provide their particular efficacies, liquid chromatographic methods have been developed and validated to accommodate their differences in chemical, biological and physical behaviors. For instance, while it is sufficient for an HPLC potency assay and purity determination to describe the quality of many small molecules in aqueous, buffer, organic solvent solutions, large biomolecules such as proteins must be tested differently, taking care not to disrupt not only the primary amino acid structure, but secondary and tertiary [conformations] so that denaturation is avoided and the molecule will retain its chemical composition, shape, size and volume. The need to characterize a rather fragile, large, three-dimensional macromolecule necessitates that a profile of test results be obtained from a variety of test methods.

Such language makes it clear, even in 2007, that techniques and analyses useful on large molecules would not be considered suggestive of utility with small molecules. Given the distinct structural and conformational characteristics of large molecules as compared to small molecules and given the caveat in Exhibit B "not to disrupt not only the primary amino acid structure, but secondary and tertiary conformations [of a large molecule] so that denaturation is avoided and the molecule will retain its chemical composition", one of ordinary skill in the art would not be motivated to modify the teachings of Lee, *et al.* to arrive at the claimed methods of analysis of small molecules. In fact, the state of the art at the time the invention was made, as embodied by Exhibits A and B, constitutes a clear teaching away from the claimed invention.

Moreover, Applicants specifically invite the Examiner's attention to the session entitled: "Application of Various Analytical Techniques in the Clinical Drug Development Studies, Large Molecule vs. Small Molecule, Cross Usage of Same Analytical Method for Pharmaceutical Analysis and Bioanalytical Work. Is It Possible?" Titles of sessions such as this, make it clear that the ordinarily skilled artisan, even in the year 2007, would certainly not find the pending claims obvious in light of Lee et al.

Lastly, with respect to the detection aspect of the analysis, Applicants respectfully invite the Examiner's attention to page 5, lines 2-5, where the specification indicates that the "mass spectrometric sensitivity of the small molecules is ***significantly*** and ***surprisingly greater*** in the presence of the surfactants of the invention than in the presence of SDS at similar concentrations, even in the presence of [the] degradant products (emphasis added)." As such, even assuming *arguendo* that the analysis of large molecule suggests the use of other sized molecules is possible, it certainly would not teach or suggest that the presence of the surfactants of the invention would be surprisingly advantageous for small molecules.

Accordingly, Applicants assert that Lee et al. do not teach or suggest the advantageous analysis of small molecules in the presence of the surfactants of the instant invention, and therefore respectfully request withdrawal of the rejection of claims 1-16 under 35 U.S.C. §103(a), and favorable reconsideration.

CONCLUSION

In view of the foregoing, reconsideration and withdrawal of all rejections, allowance of the application with all pending claims, and passage of the application to issuance are earnestly solicited. If a telephone conversation with Applicants' attorney would help expedite the prosecution of the above-identified application, the Examiner is urged to call Applicants' attorney at the telephone number below.

Applicants have filed a petition for a two-month extension of time herewith, as well as authorization to charge our Deposit Account for the related fee. Applicants believe that there are no additional fees due with this response. However, if a fee is due, the Commissioner is hereby authorized to charge Deposit Account No. 04-1105 for any fee(s) due with this response.

Dated: April 4, 2008

Respectfully submitted,

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Exhibits A & B (attached)